EXHIBIT 1
PART 2 OF 2

4/28/2003

GlaxoSmithKline

Cover Letter Via Facsimile Transmission (301) 594-6771
Followed By Airborne Express with Attachments

GlaxoSmithKline
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April 28, 2003

Lesley R. Frank, Ph.D., J.D.
Regulatory Counsel
Food and Drug Administration
Division of Drug Marketing,
Advertising and Communications
HFD-42, Rm. 8B-46
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-358
Wellbutrin SR® (bupropion HCl) Sustained-Release Tablets
MACMIS #11170

Dear Dr. Frank:

This letter represents a supplemental response to your letter dated October 9, 2002, concerning Wellbutrin SR (bupropion HCl) Sustained-Release Tablets. The following narrative is GSK's response to multiple requests concerning Dr. Wolkowitz, including Request Numbers 2, 4, 5, 6, 7, 8, 9, 10, 13.

Consistent with our prior agreement, reflected in our letter of October 29, 2002, the information provided herein and responsive to your requests covers the period January 1, 2001 through October 9, 2002. We refer to this period below as the "relevant time period."

A. Background

Dr. Owen Wolkowitz is a psychiatrist and a Professor of Psychiatry at the University of California San Francisco School of Medicine and Director of the Psychopharmacology Assessment Clinic, Langley Porter Psychiatric Institute. Dr. Wolkowitz is an educator and a treating physician. Dr. Wolkowitz is a well-known psychiatrist in the San Francisco Bay Area who is regularly invited to speak on behalf of pharmaceutical research companies in educational and other forums.

Dr. Wolkowitz attended GSK P.R.I.D.E. ("Peer Review of Intimacy, Depression, and Efficacy") Speaker Training in January 2001 and is a member of GSK's Speakers Bureau. During the relevant period, Dr. Wolkowitz delivered GSK-sponsored presentations relating to Wellbutrin SR, which are described in greater detail below.

In addition, GSK retained Dr. Wolkowitz to serve as a consultant to one of GSK's advisory committees. His only service to the Company in this capacity involved attending one advisory committee meeting in January 2001.

Please be advised that the information presented below is based on interviews with Dr. Wolkowitz and information he provided at our request, and records available from GSK's Speakers Bureau. Dr. Wolkowitz has reviewed and confirmed the accuracy of the information presented below.

B. Speaker Training

GSK contracted with Dr. Wolkowitz to attend its Speaker Training for Wellbutrin SR on January 26-28, 2001. Dr. Wolkowitz was reimbursed for expenses incurred for his travel. Following the January 2001 Speaker Training, GSK provided the speaker training slides shown during the meeting to Dr. Wolkowitz. In our initial submission, dated November 14, 2002, we provided the material related to the January 2001 Speaker Training programs, including the slides shown at the meeting and subsequently provided to attendees that requested them, including Dr. Wolkowitz. *See* Letter of November 14, 2002 at 2, and Appendix A thereto; *see also* Letter of December 23, 2002 at 8, and Appendix N thereto.

As we noted in our submission of February 28, 2003, GSK's Speaker Training Program slides contain information about weight loss associated with Wellbutrin SR to educate physicians about weight loss potential and to prompt physicians to consider those consequences when treating and managing depression. The presence of this important information about the effect of the product on weight, however, should not be construed as promoting Wellbutrin SR for weight loss or obesity.

In addition to attending the January 2001 P.R.I.D.E. Speaker Training, on February 7, 2002, Dr. Wolkowitz attended speaker training provided by a Regional Medical Scientist ("RMS") as a refresher to his initial January 2001 training. Dr. Wolkowitz was not compensated for attending the RMS training.

C. Speaker Program Events

Dr. Wolkowitz was a member of GSK's Speakers Bureau during the relevant time period. From January 2001 through October 2002, Dr. Wolkowitz delivered approximately eighteen (18) presentations at GSK's P.R.I.D.E. events for Wellbutrin SR. Additional information about Dr. Wolkowitz's P.R.I.D.E. speaker events are listed in Appendix A, attached hereto. As noted in our February 28, 2003 submission, GSK sales representatives selected the venue, date, and time, identified Dr. Wolkowitz as the speaker, extended invitations to prospective attendees, and selected the topic from a

list of six established topics.[1] *See* Letter of February 28, 2003, at 6. GSK contracted with a third party, SCS Healthcare Marketing, to coordinate the P.R.I.D.E. events and handle the related administrative duties.

In addition to P.R.I.D.E. speaker events, Dr. Wolkowitz also spoke on behalf of GSK on approximately thirty-one (31) occasions during the relevant time period on topics relating to Wellbutrin SR. These events are further identified in Appendix B, attached hereto. As described in our February 28 submission, these events were generally initiated by a GSK sales representative who would invite Dr. Wolkowitz to speak to healthcare professionals about Wellbutrin SR. The sales representative would also arrange and host these speaking events. *See* Letter of February 28, 2003, at 6-7.

During the course of interviewing and obtaining information from Dr. Wolkowitz, he reported that he independently developed and typically uses a standard presentation when asked to speak about treating depression by pharmaceutical manufacturers that market antidepressants. Dr. Wolkowitz's standard presentation is titled, "Rational Use of the New Generation Antidepressants: Maximizing Efficacy and Minimizing Side Effects." A copy of this presentation is attached hereto at Appendix C. Because Dr. Wolkowitz is a well-known psychiatrist in the San Francisco Bay area, he is often invited to speak on behalf of other pharmaceutical research companies in addition to GSK. In presentations on behalf of other pharmaceutical research companies, Dr. Wolkowitz typically uses this standard presentation for all speaker events related to antidepressants regardless of the sponsoring company. Dr. Wolkowitz's standard presentation contains information that he developed about multiple antidepressants. Dr. Wolkowitz may omit certain slides depending on the topic, but the overall presentation is the same.

Dr. Wolkowitz developed his standard presentation using information obtained from published literature, GSK, and other pharmaceutical companies that market antidepressants. Some of the information included in the presentation relating to the effect of Wellbutrin on body weight was taken from other material that Dr. Wolkowitz obtained from GSK either during speaker training or in response to unsolicited requests for information. As with other healthcare professionals to whom GSK provided such information (either during speaker training or in response to unsolicited requests), GSK disclosed on such documents that the material includes information relating to unapproved indications for educational or training purposes only. Except to the extent that GSK provided material that Dr. Wolkowitz decided to use in developing his standard presentation, the Company did not participate in preparing, developing, or publishing the presentation.

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[1] The six established topics are: (1) Choosing an Antidepressant for the Long Haul; (2) Using Wellbutrin SR® in the Primary Care Setting; (3) Depression, Antidepressants, and Sexual Dysfunction; (4) Depression and Intimacy: Strategies for Discussing Sexual Dysfunction with Patients; (5) Issues in the Management of Depression; and (6) Options for the Primary Care Treatment of Depression.

During the course of this review, I obtained Dr. Wolkowitz's standard presentation and discovered it contained phrases and information about the effect of Wellbutrin SR on body weight that some may consider as outside the product's approved indication. Dr. Wolkowitz includes a prominent note to the audience on the first slide of his standard presentation that some of the uses discussed therein may not be FDA-approved. However, despite Dr. Wolkowitz's note, I promptly asked Dr. Wolkowitz to refrain from using this presentation in all GSK-sponsored events. As a precautionary measure, GSK also postponed Dr. Wolkowitz's scheduled speaking engagements until I was able to discuss the issues involved in his presentations, and gain his commitment that he would no longer use information that may be considered outside the approved indication for Wellbutrin SR in his presentations. Dr. Wolkowitz cooperated fully with the Company and made the requested commitment.

In speaking with Dr. Wolkowitz about his standard presentation and the information contained therein relating to the effect of the product on body weight, he made it clear that he does not directly or indirectly communicate or suggest in his presentations that Wellbutrin SR should be used either for weight loss or to treat obesity. Dr. Wolkowitz credibly explained the information is intended solely to educate physicians about the physiological effect of several antidepressants including Wellbutrin SR on the body weight of depressed patients. Dr. Wolkowitz further explained that if a patient's depressed state is associated closely with weight loss or weight gain, the effect of a particular antidepressant on weight is an important consideration for the treating physician in developing an informed recommendation about the appropriate therapeutic drug to prescribe.

GSK did not pay the audience to attend these speaker events or reimburse their expenses, except for parking fees in some cases. The events were typically attended by approximately 5 to 30 physicians, psychiatrists, and other health care professionals. The audience was aware at the time of the presentation that GSK sponsored the event. Dr. Wolkowitz was paid for each event in accordance with his agreed-upon fee schedule for the speaker events and reimbursed for out-of-pocket expenses incurred, such as travel expenses and parking fees. GSK is not aware of the creation or availability of any audiotape, videotape, or transcript of these presentations.

D. Independent Medical Education

In addition to GSK-sponsored non-independent speaker events, Dr. Wolkowitz also spoke at independent, non-promotional speaker programs that were sponsored by GSK. For example, Dr. Wolkowitz spoke at five GSK-sponsored continuing medical education ("CME") events during the relevant time period. Two of the events were Medical World Conference Saturday Symposia programs and three were "Grand Rounds" events conducted at local San Francisco Bay-area hospitals. Details about those speaking engagements are provided below.

On June 1, 2002, Dr. Wolkowitz presented a segment of a Saturday Symposia conference titled, "Understanding Depression: matching the Neurotransmitter to the Patient", in San Jose, California. On June 29, 2002, Dr. Wolkowitz provided the same presentation at a Saturday Symposia in Sacramento, California. Medical World Conference ("MWC") handled all of the administrative functions associated with the Saturday Symposia programs and GSK provided funding. Except to the extent that GSK provided slides and related information that Dr. Wolkowitz decided to incorporate in his presentation, the Company did not have any involvement with, or influence on the initiation, preparation, development, or publication of the materials presented. Details about the Saturday Symposia programs were also provided in GSK's response dated February 28, 2003. *See* Letter of February 28, 2003 at 7-8. CME credit for the Saturday Symposia events was provided by MWC.

GSK is not aware of the creation or availability of any audiotape, videotape, or transcript of these CME presentations by Dr. Wolkowitz. However, Dr. Wolkowitz provided GSK with a copy of the audience evaluations from these events, which are attached. *See* Medical World Conference CME Evaluation Form Results for June 1, 2002 and June 29, 2002 events attached at Appendix D. As you will note, the audience scored Dr. Wolkowitz's presentations very favorably in the "free of commercial bias" category.

On July 9, 2001, Dr. Wolkowitz presented at Grand Rounds in the Department of Psychiatry at St. Francis Hospital in San Francisco, California on the topic: "Managing Depression and Maximizing Effectiveness and Minimizing Side Effects." Approximately 10-15 psychiatrists attended this event. On January 23, 2002, at Ground Rounds at Sutter Hospital in Santa Rosa, California, Dr. Wolkowitz delivered his standard presentation ("Rational Use of the New Generation Antidepressants: Maximizing Efficacy and Minimizing Side Effects"). There is no record of the number of attendees. On July 26, 2002, Dr. Wolkowitz again delivered his standard presentation at Grand Rounds in the Department of Medicine at Santa Clara Valley Medical Center in San Jose, California. Approximately 100 residents, medical students, faculty, and internal medicine physicians attended this event.

The "Grand Rounds" events were advertised by organizers of the events at the respective hospitals through posted flyers and similar medium. The events were open to all health care professionals at the hospital. Dr. Wolkowitz selected the topic for these events. GSK did not prepare, develop, or publish his presentations. The audience received CME credit for the event which was provided presumably by the hosting institution. GSK did not pay the audience to attend these events or reimburse their expenses. The audience was aware at the time of the presentation that GSK sponsored the event. GSK is not aware of the creation or availability of any audiotape, videotape, or transcript of these CME presentations.

E. Advisory Committee Activities

GSK retained Dr. Wolkowitz as a consultant to attend one advisory committee meeting related to Wellbutrin SR on January 11-14, 2001. The event was a meeting of the Serotonin Special Issues Board ("SIB"), a local advisory board, that focused on Serotonin Receptor Pharmacology. Local advisory boards are designed to bring leading local physicians together so that GSK may obtain advice and feedback from these consultants on a variety of issues, including strategies for business development and other commercial issues, relating to Wellbutrin SR. GSK provided detailed information about local advisory boards in its February 28 submission. *See* Letter of February 28, 2003, at 8-9. The Serotonin SIB meeting was divided into three sessions as they relate to serotonin: (1) depression; (2) irritable bowel syndrome; and (3) migraines. The meeting was attended by specialists in the area of gastroenterology, psychiatry, and neurology with expertise in the therapeutic areas affected by serotonin/neurotransmitter receptor pharmacology. Dr. Wolkowitz attended the meeting only as a consultant and did not moderate or speak at the meeting. Dr. Wolkowitz received a consultation fee of $1,000.00 and was reimbursed for his out-of-pocket expenses. Dr. Wolkowitz has not engaged in any other advisory board consulting or other activities for GSK related to Wellbutrin SR.

F. No Promotion of Wellbutrin SR for Weight Loss

Other than the above-described activities, Dr. Wolkowitz has not had any involvement in assisting GSK with respect to sales or marketing of Wellbutrin SR. Dr. Wolkowitz frequently speaks about Wellbutrin SR on behalf of GSK, but, as discussed above, Dr. Wolkowitz does not promote Wellbutrin SR for weight loss or treatment of obesity. In some cases, Dr. Wolkowitz's presentations contain information about the effect of Wellbutrin SR on weight. Educating physicians about the weight loss potential associated with Wellbutrin SR is important to ensure that physicians appropriately prescribe the product in depressed patients and consider weight changes. As a speaker, Dr. Wolkowitz is responsible for educating his audience about the weight loss issues associated with Wellbutrin SR so that they are adequately informed and can safely and effectively treat their patients.

Most importantly, GSK has not asked or encouraged Dr. Wolkowitz to promote Wellbutrin SR for weight loss or treatment of obesity. Dr. Wolkowitz developed his presentation slides independently. GSK did not participate in preparing, developing, or publishing Dr. Wolkowitz's presentation materials. In fact, when I became aware of information in Dr. Wolkowitz's presentation materials that could be considered by some as outside the product's approved indication, I asked Dr. Wolkowitz to refrain from using the presentation and postponed his speaking engagements until the Company had an opportunity to discuss these issues with Dr. Wolkowitz and he agreed to comply with the Company's requests. We have spoken with Dr. Wolkowitz on several occasions and have found him to be responsive and sincere. We believe Dr. Wolkowitz now has a

clear understanding of what is required when he speaks about GSK products at GSK-sponsored events. Indeed, during his review of this description, Dr. Wolkowitz confirmed that when he speaks at GSK-sponsored promotional events, he only uses the currently approved GSK slide set -- not his individually-developed presentation -- except in response to specific unsolicited questions from the audience. Our analysis of his presentations makes clear that Dr. Wolkowitz has never promoted Wellbutrin SR for weight loss or to treat obesity, and his presentations have been aimed at providing healthcare professionals with objective, scientific information about the treatment of depression.

* * * *

The representations made in this response are based on our information and belief. If we become aware of additional or new information that materially alters the accuracy of these responses, we will supplement these responses.

Please note that all materials and information provided in response to your requests and marked "GSK Confidential/Proprietary" are confidential and proprietary to GSK, and as such, are protected under the applicable provisions of 18 U.S.C. 1905 or 21 U.S.C., Section 331(j), and all accompanying regulations. Additionally, GSK is providing all information and documents to the Division of Drug Marketing, Advertising and Communications for its use during this inquiry only.

Sincerely,

Lauren C. Stevens by SLS

Lauren C. Stevens
Vice President and
Associate General Counsel
US Legal Operations

Enclosures: Appendices A, B, C and D

5/21/2003

GlaxoSmithKline

Cover Letter Via Facsimile Transmission (301) 594-6771
Followed By Airborne Express with Attachments

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May 21, 2003

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Re: NDA 20-358
Wellbutrin SR® (bupropion HCl) Sustained-Release Tablets
MACMIS #11170

Dear Dr. Frank:

This letter represents our final supplemental response to your letter dated October 9, 2002 concerning Wellbutrin SR (bupropion HCl) Sustained-Release Tablets. We are providing supplemental information and documentation responsive to Requests 13 and 14. As this will be our last submission, we are also providing a Conclusion that summarizes the information we have provided to date.

Consistent with our prior agreement, reflected in our letter of October 29, 2002, the information provided herein and responsive to your requests covers the period January 1, 2001 through October 9, 2002. We refer to this period below as the "relevant time period."

Supplemental Response to Request No. 13

Describe (a) any information, data, studies, instructions, directions, guidelines, proposed comments or answers, or other statements or materials relating to the use or potential use of Wellbutrin SR in connection with weight loss, or any potential weight loss effect of Wellbutrin SR, and (b) any information, instructions, directions, proposed comments or answers, or other guidance or materials relating to the promotion or discussion of off-label uses for Wellbutrin SR, provided to Dr. Donna Ryan, Dr. Owen Wolkowitz, Dr. James Anderson, any of the individuals or entities identified in item 3 above, or any attendee at any speaker training program.

In our prior submissions dated December 23, 2002, February 28, 2003, and April 28, 2003, we provided information in response to Request No. 13. We are supplementing our response with the additional information presented below.

In addition to the information already provided regarding materials relating to Wellbutrin SR and weight loss, GSK's Medical Information Department developed responsive letters ("MI letters") and slides relating to the use of Wellbutrin SR, including a MI letter and slide set titled, "Effects of Wellbutrin SR on Body Weight." A copy of the MI letter and slide set are attached at Appendix A and B.

These materials are used to educate and inform health care professionals who submit unsolicited requests for educational information on this topic to the Company. They are not used to promote the product. Both the slides and the MI letter bear a prominent disclosure that the information contained therein may be considered outside the U.S. labeling for the product. For example, the slides include an introductory slide that contains the following prominent statement:

> These slides are intended as an educational service to respond to the requests or searches by U.S. healthcare professionals and are not intended as medical advice. These slides may not represent a comprehensive review of this topic. Some of the information in these slides may be outside of the U.S. labeling for our products. These slides are not intended to offer an opinion on the advisability of administering our products in a manner inconsistent with product labeling.

The MI letters contain a similar, prominent bolded disclosure on the first page, which states as follows:

> Some of the information contained in this letter may be outside the product labeling for Wellbutrin SR. This letter is not intended to offer an opinion on the advisability of administering Wellbutrin SR in a manner inconsistent with product labeling. In order to allow GlaxoSmithKline to monitor the safety of Wellbutrin SR, we encourage clinicians to report suspected overdoses or adverse effects to our Product Surveillance Department (1-888-825-5249). Please consult the enclosed product information for full prescribing details.

These disclosures make clear that the Company provides this information in response to unsolicited requests, that the material is intended only to educate health care professionals, and not intended to promote the product.

Moreover, GSK's Medical Information Department provides these materials to physicians only in response to an unsolicited request in accordance with FDA guidance

and GSK internal policy. The Medical Information Department's procedure for providing materials in response to unsolicited requests is described in detail in our previous submission dated December 23, 2002.

Supplemental Response to Request No. 14

With respect to the "Speaker Training Slides for Wellbutrin SR" dated December 2001:

a. **describe the purpose and usages for these slides;**

b. **identify all persons who participated in the preparation, revision, supervision and approval of these slides;**

c. **identify each presentation or event at which these slides were shown, presented, or otherwise used at which persons not employed by GSK were present; describe the purpose of such presentation or event, and identify the number and nature of the attendees at such event;**

d. **describe any distribution of these slides to any person or entity outside of GSK;**

e. **provide any other versions of this presentation, and any handouts, notes, manuals, instructions, or other materials used in conjunction with these slides at any event or presentation.**

In our December 23, 2002 submission, we provided details associated with the development and distribution of the December 2001 Speaker Training Kit, a version of which we believe you reference in your October 2002 information request. We noted in our December 23 response that after the December 2001 Speaker Training meeting, GSK's Medical Information department created a shortened version of the slide set presented during the meeting by eliminating most of the business-oriented and individual presenter introductory slides. This shortened version of the December 2001 slides is referred to as the "Abbreviated WBSR STP Slides" and the one we believe you refer to in your October 9, 2002 letter as the "'Speaker Training Slides for Wellbutrin SR,' dated December 2001."

We also explained in our December 23 submission that Regional Medical Scientists ("RMSs"), who are medical professionals independent of the sales/marketing organization, believed that the Abbreviated WBSR STP Slides was the slide lecture kit that they were to provide physician/trainees for use in non-independent presentations for GSK. However, GSK intended that this kit be used only for training purposes at the December 2001 meeting and to fulfill specific requests for slides submitted by those

attending that meeting. GSK did not intend for those slides to be used in affirmative presentations by GSK-sponsored speakers. You may recall that speakers trained by RMSs were required to sign an agreement prior to speaking for GSK that required them to confine their affirmative presentations to approved product indications, and that the second slide of the Abbreviated WBSR STP Slides reminds physicians of this obligation.

During our telephone conversation of January 21, 2003, you asked that we provide some additional information about the distribution of the Abbreviated WBSR STP Slides. Following your request, we have determined that approximately 250 individuals received a version of the Abbreviated WBSR STP Slides. Of those, at least 80 physicians received the slides in response to an unsolicited, specific request. The remaining physicians received the slides because they attended regional RMS training and were provided the slides following such training.

As we noted in our December 23 response, after learning of the distribution of the Abbreviated WBSR STP Slides, the Company promptly developed and implemented a series of actions to instruct the 169 RMS-trained physicians that they not use these slides in their affirmative presentations. These steps included notifying RMS-trained physicians and instructing them not to use the Abbreviated WBSR STP Slides when speaking on behalf of GSK and a specific direction not to use the slides in affirmative presentations. We also provided these physicians with a replacement slide kit containing on-label information only.

Conclusion

Your letter dated October 9, 2002 requested that GSK voluntarily provide comprehensive information about its promotion of Wellbutrin SR. The letter made clear that the focus was whether GSK has engaged in the promotion of Wellbutrin SR for weight loss. The broad scope of the information requested and the identification of three physicians in the letter suggested that DDMAC had obtained information about the promotion of Wellbutrin SR warranting further investigation. We must tell you that we were surprised by both the request and the apparent concern about the promotion of the product for weight loss.

Nonetheless -- and without prejudging the matter -- we systematically and carefully collected, reviewed, and provided you with extensive information and supporting documentation regarding GSK's promotional and non-promotional activities relating to Wellbutrin SR and weight loss. This was a significant undertaking involving substantial time and resources because it required us to locate the requested information and develop descriptive information to enable DDMAC to gain a better understanding of the manner in which GSK trains and uses speakers and promotes Wellbutrin SR. For example, most of the information you sought on the three physicians

named in your October 9 letter was obtained only through interviews with the physicians. They were the only available source to obtain some of the information sought. Obviously, we collected this information and conducted these activities for the purpose of cooperating and responding to DDMAC's wide-ranging request. In the final analysis, all of the information consistently and clearly points to the same conclusion -- GSK has not developed, devised, established, or maintained any program or activity to promote, either directly or indirectly, the use of Wellbutrin SR to achieve weight loss or treat obesity.

Like other responsible pharmaceutical research companies, GSK recognizes the importance of continuing to educate health care professionals about its products beyond the information provided in the FDA-approved prescribing information. In response to DDMAC's October 9 request, we provided extensive information describing the programs, presentations, and other activities developed by GSK to educate and inform physicians and other health care professionals about the clinical management of depression and the use of Wellbutrin SR. We found that GSK has not developed or maintained promotional plans or activities to directly or indirectly promote Wellbutrin SR for weight loss or the treatment of obesity. As you know, the FDA-approved Prescribing Information contains a precaution regarding the anorectic and/or weight-reducing potential associated with Wellbutrin SR. It further advises physicians to consider this potential if weight-loss is a major presenting sign of a patient's depressive illness. Thus, educating psychiatrists and primary care physicians about the weight loss potential associated with Wellbutrin SR is important to ensure that physicians consider weight issues when prescribing the product to depressed patients. For example, to educate physicians about the drug's weight loss potential and to prompt consideration of those consequences, GSK's P.R.I.D.E. ("Peer Review of Intimacy, Depression, and Efficacy") Speaker Training slides contain information about weight loss associated with Wellbutrin SR. Similarly, the Company also developed the MI letter referenced above in the supplemental response to request 13 solely for the purpose of responding to physicians about the effect of the product on weight because weight loss is an important consideration, and a common question that arises from healthcare professionals who treat patients with depression. Importantly, this material does not promote Wellbutrin SR for weight loss and is provided only in response to specific, unsolicited requests by individuals for information, consistent with established FDA guidance.

As noted above, the October 9 letter also requested detailed information on the activities of three specifically-named physicians, Drs. Donna Ryan, Owen Wolkowitz, and James W. Anderson. In response, we conducted thorough interviews with these physicians and collected extensive information regarding their activities relating to Wellbutrin SR. We found that none of these three individuals engaged in the promotion of Wellbutrin SR for weight loss or treatment of obesity. We also found that (1) GSK did not participate in the initiation, preparation, development, or publication of the physicians' presentation materials; (2) the physicians' audiences were aware that GSK

sponsored and supported these presentations; and (3) except to the extent that Dr. Wolkowitz delivered non-independent presentations on behalf of GSK, these physicians are not involved with sales or marketing of Wellbutrin SR. We provided you with the information and documentation that clearly supports these findings.

After reviewing and considering the information related to these physicians, we have concluded that any allegation that they are involved in the off-label promotion of Wellbutrin SR for treatment of obesity cannot be substantiated. We have found no basis for any significant concern about the activities they conducted related to Wellbutrin SR. Drs. Anderson and Ryan did not participate in any promotional presentations for GSK. Although Dr. Wolkowitz was a trained speaker and delivered non-independent presentations using a script he independently developed, Dr. Wolkowitz made it absolutely clear that the information in his presentation about the effect of the product is solely for educational purposes and that he does not suggest directly or indirectly that Wellbutrin SR should be used for weight loss. We also have found no connection among these three physicians, and welcome FDA to share with us any information it may have that is contrary to what we have provided regarding the three physicians. If FDA has information that contradicts what we have provided, we will immediately review and investigate this information.

You also asked GSK to provide detailed information regarding its speaker training programs and speaker training slide kits, including detailed information on the provision of slide kits to health care professionals. We found that the Wellbutrin SR speaker training slide kit that we believe to be of concern to you, the "Abbreviated WBSR STP Slides," was provided only to healthcare professionals who attended RMS-training or who submitted an unsolicited request for these specific slides. As we have described in previous submissions, we have taken appropriate action to correct the distribution of this slide kit by the RMSs to RMS-trained physicians.

You also questioned the extent to which GSK utilized its trained speakers to evaluate the legitimacy of the Company's speaker training. We provided detailed information on speaker training, enrollment in the GSK Speakers Bureau, and presentations by trained speakers. It shows that 89.5% of the health care professionals who attended any Wellbutrin SR Speaker Training enrolled in the GSK Speakers Bureau and delivered at least one presentation during the relevant period. Of the 262 physicians who attended the national P.R.I.D.E training during January 2001 and December 2001, 95% made at least one presentation relating to Wellbutrin SR. This objectively demonstrates that GSK's training program was legitimate and intended to prepare speakers to deliver presentations.

GSK recognizes that Wellbutrin SR has not been approved for weight loss or treatment of obesity and may not be promoted for those uses. As such, GSK promotes Wellbutrin SR for its approved indication as an effective first-line agent for the treatment

of depression with a low incidence of sexual dysfunction and weight gain. GSK's promotional material and activities for Wellbutrin SR are consistent with the approved Prescribing Information and the supporting clinical data. All of the documentation and materials we have reviewed and provided to you during the course of this inquiry support this conclusion.

In the course of responding to your requests, we became aware of certain activities that were inconsistent with GSK policy. Rather than attempt to justify these activities, the Company took its responsibilities seriously and instituted appropriate and necessary corrective actions to address these activities. We have provided you with information and documentation related to these corrective activities in our previous submissions. By way of example, as discussed above in this response and in our December 23, 2002 submission, we took prompt and effective corrective action to prevent the use of the abbreviated December 2001 Speaker Training slides containing information not intended for affirmative presentations when we learned it was provided by RMSs to physicians for use in non-independent presentations. GSK has taken this inquiry as an opportunity to review our programs and activities for Wellbutrin SR and take action where appropriate to ensure that Wellbutrin SR is promoted consistent with the approved Prescribing Information and the supporting clinical data.

The extensive information that we have provided in response to your comprehensive request of October 9, 2002 and related conversations, objectively demonstrates that GSK has not engaged in the promotion of Wellbutrin SR for weight loss. After you consider the information we have provided, we believe that you will reach this conclusion as well.

* * * *

The representations made in this response are based on our information and belief. If we become aware of additional or new information that materially alters the accuracy of these responses, we will supplement these responses.

Please note that all materials and information provided in response to your requests and marked "GSK Confidential/Proprietary" are confidential and proprietary to GSK, and as such, are protected under the applicable provisions of 18 U.S.C. § 1905 or 21 U.S.C. § 331(j), and all accompanying regulations. Additionally, GSK is providing all information and documents to the Division of Drug Marketing, Advertising and Communications for its use during this inquiry only.

With this final submission, we complete our production of information and documents in response to the requests in your letter dated October 9, 2002 and additional requests raised in your teleconference with GSK on January 21, 2003 concerning Wellbutrin SR. After you have an opportunity to review the materials we have provided, we would like to arrange a teleconference with you at your convenience to discuss any final questions that you may have. I will contact you within the next week to determine when we can schedule the teleconference. If you have any additional questions, please do not hesitate to contact me directly at your convenience at (919) 483-2205.

Sincerely,

Lauren C. Stevens
Vice President and
Associate General Counsel
US Legal Operations

Enclosures: Appendices A and B

11/6/2003

GlaxoSmithKline

Cover Letter Via Facsimile Transmission (301) 594-6771
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November 6, 2003

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Re: NDA 20-358
Wellbutrin SR® (bupropion HCl) Sustained-Release Tablets
MACMIS #11170

Dear Dr. Williams:

As you know, by way of a letter dated October 9, 2002, DDMAC requested that GlaxoSmithKline ("GSK") voluntarily provide comprehensive information about its promotion of Wellbutrin SR® (bupropion HCl) Sustained Release tablets. The purpose of the letter was to enable DDMAC to evaluate whether GSK engaged in the promotion of Wellbutrin SR for weight loss or as a treatment for obesity.

DDMAC's October 9 letter prompted GSK to systematically and carefully collect, review, and provide extensive information and supporting documentation regarding independent and non-independent activities supported by GSK and relating to Wellbutrin SR. In compiling the requested information, we became aware of some activities that were inconsistent with GSK policy, including certain presentation topics and presentations delivered by physician speakers that contained information outside the approved product labeling. As a responsible company committed to compliance, GSK promptly took appropriate corrective action to address those activities. Through our responses to the October 9 letter, we indicated that GSK had taken the Division's inquiry as an opportunity to review our programs and activities for Wellbutrin SR and take action where appropriate to ensure Wellbutrin SR is promoted consistent with the approved Prescribing Information and supporting clinical data. Although there were isolated deficiencies, the objective evidence clearly demonstrates that GSK has not developed, maintained, or encouraged promotional plans or activities to promote, directly or indirectly, Wellbutrin SR for weight loss, the treatment of obesity, or any other unapproved indication.

After our May 2003 submission, one of our sales representatives in Oregon, Aldo Davico, disclosed to us that he had alleged in a letter dated June 9, 2003 to DDMAC that GSK had engaged in off-label promotional activity for Wellbutrin SR.[1] In his June 9 letter, Mr. Davico claims that two physicians delivered presentations on behalf of GSK and promoted the use of Wellbutrin SR for the treatment of obesity and other off-label indications. Mr. Davico told us that he attached to his June 9 letter presentations used by Drs. Ken Fujioka and James Hudziak in GSK speaking engagements that he (Mr. Davico) organized and attended. For your convenience, we have attached copies of the June 9 letter and the presentations Mr. Davico told us he provided to DDMAC.

GSK has independently investigated Mr. Davico's allegations through a review of the physicians' presentations, as well as interviews of Mr. Davico and other GSK employees with whom he regularly worked, including his district sales manager, an associate sales representative and regional market development managers. In sum, these allegations do not present any new issues; in responding to DDMAC's October 9 letter, we stated in our letter of March 28 that GSK undertook measures to prevent future presentations involving Wellbutrin SR from reflecting terms or uses that could be outside the approved indication. We are taking this opportunity to share our findings and other relevant information that DDMAC should consider in evaluating the merits of Mr. Davico's allegations.

First, we acknowledge that the physicians' presentations Mr. Davico provided contain information outside the FDA-approved indication for Wellbutrin SR. GSK recognized during the past year that some physicians had independently developed presentation slides containing such information despite a provision in their speaker contract related to compliance with FDA requirements and guidance. GSK took the appropriate corrective actions in 2002 and early 2003 to effectively address the issue. This included direct communications to certain physicians reminding them of the requirements associated with speaking on behalf of the Company. We also required some physicians to execute a renewed commitment to comply with FDA and GSK requirements to confine the content of affirmative presentations to information consistent with FDA-approved labeling or risk being terminated from GSK's Speakers Bureau. Additionally, GSK reminded its sales force of its policy and requirements for speakers retained by the sales force when speaking at non-independent programs. Furthermore, beginning in 2003, GSK implemented a presentation at all of its Speaker Training Programs educating healthcare professional-trainees on GSK policy and the FDA rules regarding company-sponsored non-independent speaker programs. Also, Regional Medical Scientists who provide speaker training to healthcare professionals on a local basis are required to deliver similar education to the healthcare professional-trainees.

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[1] GSK hired Mr. Davico in February 2000 as a senior sales representative in Eugene, Oregon with responsibility for Wellbutrin SR and other GSK products. Mr. Davico is no longer employed by the Company as of November 5, 2003.

Second, in July 2001, GSK held a national sales training meeting. A small portion of this meeting was to educate and update sales representatives about the effect of Wellbutrin SR on weight and recently published data on the issue. At the meeting, Dr. Fujioka, a clinical investigator in a GSK-funded study related to weight loss, delivered a presentation on the effect of Wellbutrin SR on weight to GSK sales representatives. Although sales representatives were not encouraged to use Dr. Fujioka as a speaker for Wellbutrin SR, either during or following the training, Mr. Davico arranged for Dr. Fujioka to deliver presentations on June 1 and 2, 2002, in Eugene, Oregon. Mr. Davico did not report to GSK that Dr. Fujioka's presentation on these dates was inconsistent with the product labeling for Wellbutrin SR. Once Mr. Davico reported the issues regarding Dr. Fujioka's presentation to the Company (summer 2003), GSK investigated Mr. Davico's allegations and subsequently removed Dr. Fujioka from the GSK Speakers Bureau. Please note, however, that Dr. Fujioka had not spoken at a GSK-sponsored non-independent speaker program since January 2003.

Dr. Hudziak is a psychiatrist and a GSK-trained P.R.I.D.E. ("Peer Review of Intimacy, Depression, and Efficacy") speaker. Mr. Davico retained him for two speaking events in April and June 2002 in Eugene, Oregon. During these meetings, Dr. Hudziak delivered a presentation using slides that he had independently prepared. These slides contained information on unapproved uses for Wellbutrin SR in violation of GSK's policy. Around this same time period, GSK independently learned that Dr. Hudziak was using inappropriate material in his slide presentations. As a result, GSK investigated this matter and worked with Dr. Hudziak to remind him that he must refrain from affirmatively discussing Wellbutrin SR for unapproved uses in compliance with his signed speaker contract. Dr. Hudziak agreed to this condition. Since that time, GSK has periodically reviewed Dr. Hudziak's speaking activity and has confirmed that his slide presentations for Wellbutrin SR are consistent with its approved use.

Third, since October 2002, Mr. Davico has been engaged in a formal employment discrimination dispute with GSK. The Company first learned about his allegations of off-label promotion in June 2003 during the ongoing dialogue about his employment dispute when he disclosed to GSK his complaint to DDMAC. In a recent interview with Mr. Davico, he explained that he filed the June 2003 complaint with DDMAC not because of any ongoing concern about GSK's current promotional practices, but simply because of his mounting frustration with the Company due to his employment dispute. He specifically reported that he decided to send the complaint to DDMAC because he had "lost faith in the Company" and "did not want to be part of the organization anymore" due to his frustration with his employment dispute. It is noteworthy that Mr. Davico arranged and attended the presentations by Dr. Fujioka and Dr. Hudziak in April and June 2002, yet failed to report any concern about these physicians' presentations to anyone within GSK as required by the corporate compliance program.

Fourth, the 2002 presentations by Dr. Fujioka and Dr. Hudziak do not substantiate Mr. Davico's allegation that GSK promoted Wellbutrin SR for either obesity or any other unapproved indication. The use of Dr. Fujioka as a promotional speaker was not appropriate, and his presentation was inconsistent with Company policy and his speaker's agreement with GSK. Appropriate action was taken to remove Dr. Fujioka from GSK's Speaker's Bureau. Similarly, although Dr. Hudziak independently developed inappropriate slides, GSK recognized and instituted effective remedial action more than a year ago. The corrective actions and controls we implemented to address instances of nonconforming speaker events demonstrate GSK's ongoing commitment to promote Wellbutrin SR consistent with its approved labeling.

Fifth, during GSK's interview of Mr. Davico, he stated that he understood that promotion of a product for unapproved uses violates FDA requirements and GSK policy. Mr. Davico has also received training on GSK drug promotion policies, which clearly state promotion of unapproved uses is prohibited. Mr. Davico also repeatedly acknowledged that he was aware of off-label promotion in these speaker presentations. Despite this awareness, Mr. Davico never expressed any concern to anyone at GSK about the nature or content of the presentations delivered by Dr. Hudziak and Dr. Fujioka until he informed us of his letter to FDA. Each of the individuals GSK interviewed, all of whom have a relationship and regular contact with Mr. Davico, including his manager, confirmed that Mr. Davico had never made any statement or otherwise indicated to them that he had concerns about GSK's promotional activity for Wellbutrin SR. Furthermore, none of these individuals is aware that Wellbutrin SR is promoted for any unapproved indication. Mr. Davico also admitted during his interview that no one at GSK ever specifically advised him to promote Wellbutrin SR off-label.

GSK has thoroughly investigated Mr. Davico's allegations of off-label promotional activity for Wellbutrin SR as disclosed in his June 9 letter and determined that Mr. Davico has not introduced any new issues; GSK had already independently identified and corrected circumstances in which it became aware of non-independent physician speakers who spoke about unapproved uses for Wellbutrin SR. Furthermore, we believe that Mr. Davico's motivation for sending his June 9 letter to the FDA is part of an effort to improve his negotiating position and obtain a favorable settlement of his employment grievance.[2] We hope FDA is mindful of these circumstances when evaluating these allegations.

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[2] Mr. Davico recently alleged that he sent FDA a second letter in which he provided additional information or made further allegations related to off-label promotion. However, Mr. Davico has not disclosed to GSK the information contained in this letter as required by GSK's Code of Conduct. Therefore, we have not been able to independently investigate or substantiate his recent allegations or determine whether they are identical to allegations reflected in his June 9 letter.

The representations made in this response are based on our information and belief. If we become aware of additional or new information that materially alters the accuracy of this response, we will supplement it.

Please note that all materials and information provided and marked "GSK Confidential/Proprietary" are confidential and proprietary to GSK, and as such, are protected under the applicable provisions of 18 U.S.C. § 1905 or 21 U.S.C. § 331(j), and all accompanying regulations. Additionally, GSK is providing all information and documents to the Division of Drug Marketing, Advertising and Communications for its use during this inquiry only.

After you have an opportunity to review this information, we would like to arrange a teleconference with you at your convenience to discuss any questions that you may have. I will contact you within the next week to determine when we can schedule the teleconference. If you have any additional questions, please do not hesitate to contact me directly at (919) 483-2205.

Sincerely,

Lauren C. Stevens
Vice President and
Associate General Counsel
US Legal Operations

Enclosures